



Tumor Lysis Syndrome

Nephrology Grand Rounds

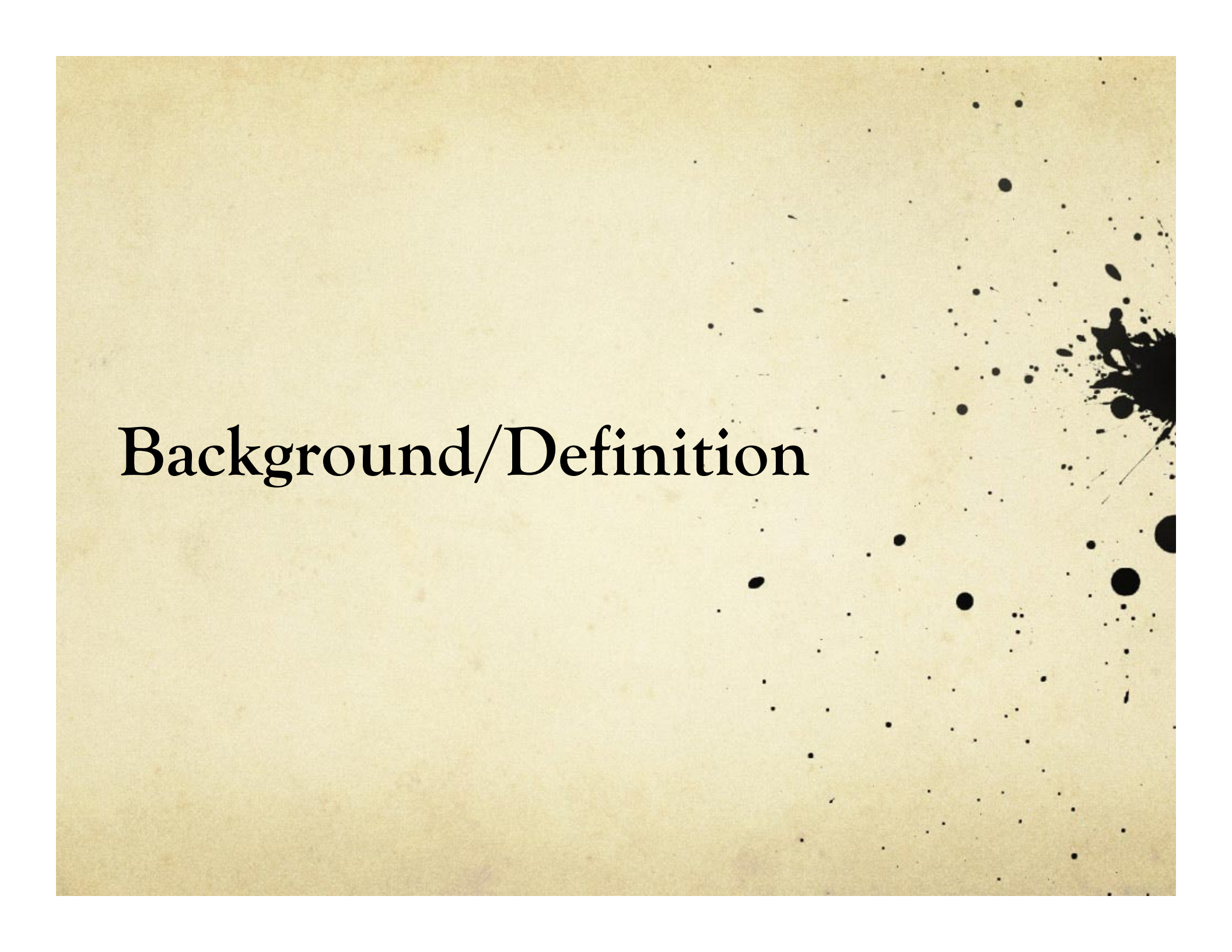
Tuesday, July 27th, 2010

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Outline

- Background/Definition
- Epidemiology/Risk Stratification
- Pathophysiology
- Treatment
- Renal Replacement Therapy

Background/Definition

The image features a light beige, textured background. On the right side, there is a prominent, dark ink splatter that spreads outwards, creating a pattern of various-sized black dots and irregular shapes. The text 'Background/Definition' is centered on the left side of the page in a black, serif font.

Background

- Tumor lysis syndrome (TLS) was first described in 1929 by Bedrna and Polcak in patients with chronic leukemia.
- TLS is an oncologic emergency caused by the rapid and massive breakdown of tumor cells, either spontaneously or after the initiation of cytoreductive therapy.
- Usually occurs in patients with bulky, rapidly proliferating, and treatment-responsive tumors.
- Although TLS can potentially occur with any type of malignancy, it is most commonly associated with acute leukemias and high-grade non-Hodgkin lymphomas (e.g. Burkitt lymphoma).

Background

- The rapid release of intracellular ions and metabolic byproducts into systemic circulation causes hyperuricemia, hyperkalemia, hyperphosphatemia, and secondary hypocalcemia.
- These metabolic abnormalities can lead to significant morbidity, putting patients at risk of severe clinical consequences that include acute kidney injury (AKI), cardiac arrhythmias, seizures, and even death.

Definition

Box 1. Cairo-Bishop Definition of Laboratory and Clinical TLS

- **Serum values included in the definition of laboratory TLS^a**
 - Uric acid ≥ 8 mg/dL or 25% increase from baseline
 - Potassium ≥ 6 mEq/L or 25% increase from baseline
 - Phosphorus ≥ 6.5 mg/dL (children) or ≥ 4.5 mg/dL (adults) or 25% increase from baseline
 - Calcium ≤ 7 mg/dL or 25% decrease from baseline
- **Criteria included in the definition of clinical TLS^b**
 - Serum creatinine ≥ 1.5 value of the upper limit of the age-adjusted normal range
 - Cardiac arrhythmia or sudden death
 - Seizure

- a. Laboratory TLS is defined by any 2 or more of the listed values within 3 days before or 7 days after initiation of chemotherapy.
- b. Clinical TLS is defined by the presence of laboratory TLS plus at least 1 of the listed features in the absence of some other cause.

Grading System

Table 2. Cairo-Bishop Clinical Tumor Lysis Syndrome Definition and Grading

Complication	Grade					
	0	1	2	3	4	5
Creatinine*†	≤ 1.5 × ULN	1.5 × ULN	> 1.5-3.0 × ULN	> 3.0-6.0 × ULN	> 6.0 × ULN	Death
Cardiac arrhythmia*	None	Intervention not indicated	Nonurgent medical intervention indicated	Symptomatic and incompletely controlled medically or controlled with device (eg, defibrillator)	Life-threatening (eg, arrhythmia associated with CHF, hypotension, syncope, shock)	Death
Seizure*	None	—	One brief, generalized seizure; seizure(s) well controlled by anticonvulsants or infrequent focal motor seizures not interfering with ADL	Seizure in which consciousness is altered; poorly controlled seizure disorder; with breakthrough generalized seizures despite medical intervention	Seizure of any kind which are prolonged, repetitive or difficult to control (eg, status epilepticus, intractable epilepsy)	Death

Epidemiology and Risk Stratification



Epidemiology

- In children with acute leukemia receiving induction chemotherapy, silent laboratory evidence of TLS occurred in 70% of cases, but clinical TLS occurred in only 3% of cases.
- In a retrospective analysis of 722 adults and children (37% non-Hodgkin lymphoma, 36% ALL, and 27% AML), the incidence of clinical TLS was 5%.
- Of patients who developed TLS, 45% had AKI, 25% required dialysis, and 15% died as a result of TLS complications.

Epidemiology

Table 3. Malignancies Commonly Diagnosed in Patients Perceived to Be at High Risk for Developing Tumor Lysis Syndrome²⁰

Malignancy	Pediatric (n = 682)		Adult (n = 387)		Total (n = 1,069)	
	No.	%	No.	%	No.	%
Acute lymphoblastic leukemia	433	63	73	19	506	47
Acute myeloid leukemia	74	11	104	27	178	17
Chronic lymphocytic leukemia	0	0	37	10	37	3.5
Chronic myeloid leukemia	6	0.9	36	9	42	4
non-Hodgkin's lymphoma	122	18	109	28	231	22
Hodgkin's disease	8	1.2	6	1.6	14	1.3
Multiple myeloma	0	0	15	3.9	15	1.4
Other hematologic malignancies	5	0.7	3	0.7	8	0.7
Solid tumors	34	5	4	1	38	3.6

NOTE. Data represent consecutive patients enrolled onto a compassionate-use trial evaluating the efficacy and safety of rasburicase in patients with cancer who presented with, or were at risk of developing, hyperuricemia.

Risk Factors

Table 4. Risk Factors for Tumor Lysis Syndrome

Characteristic	Risk Factor
Tumor type	Burkitt's lymphoma Lymphoblastic lymphoma Diffuse large-cell lymphoma ALL Solid tumors with high proliferative rates and rapid response to therapy
Tumor burden/extent of disease	Bulky disease (>10 cm) Elevated LDH (> 2× ULN) Elevated WBC (>25,000/ μ L)
Renal function	Preexisting renal failure Oliguria
Baseline uric acid	Baseline serum/plasma uric acid > 450 μ mol/L (7.5 mg/dL)
Effective and rapid cytoreductive therapy	Disease-specific therapy, varies according to tumor type

Abbreviations: ALL, acute lymphoblastic leukemia; LDH, lactate dehydrogenase.

Risk Stratification

NHL	Acute Leukemia		CLL (WBC/ μ L)	Other*	Risk
	ALL (WBC/ μ L)	AML (WBC/ μ L)			
Burkitt lymphoma, Lymphoblastic lymphoma, B-ALL	$\geq 100,000$	$\geq 50,000$ monoblastic			High
DLBCL	50,000- 100,000	10,000-50,000	10,000- 100,000 treated with fludarabine	Rapid proliferation with expected rapid response to therapy	Intermediate
Indolent NHL	$\leq 50,000$	$\leq 10,000$	$\leq 10,000$	Remainder of patients	Low

Pathophysiology



Pathophysiology

- Clinically significant TLS can occur spontaneously, but it is most often seen 48-72 hrs after initiation of chemotherapy.
- Hyperkalemia and hyperphosphatemia result directly from rapid cell lysis.
- Hypocalcemia is a consequence of acute hyperphosphatemia with precipitation of calcium phosphate (CaP) in soft tissues.

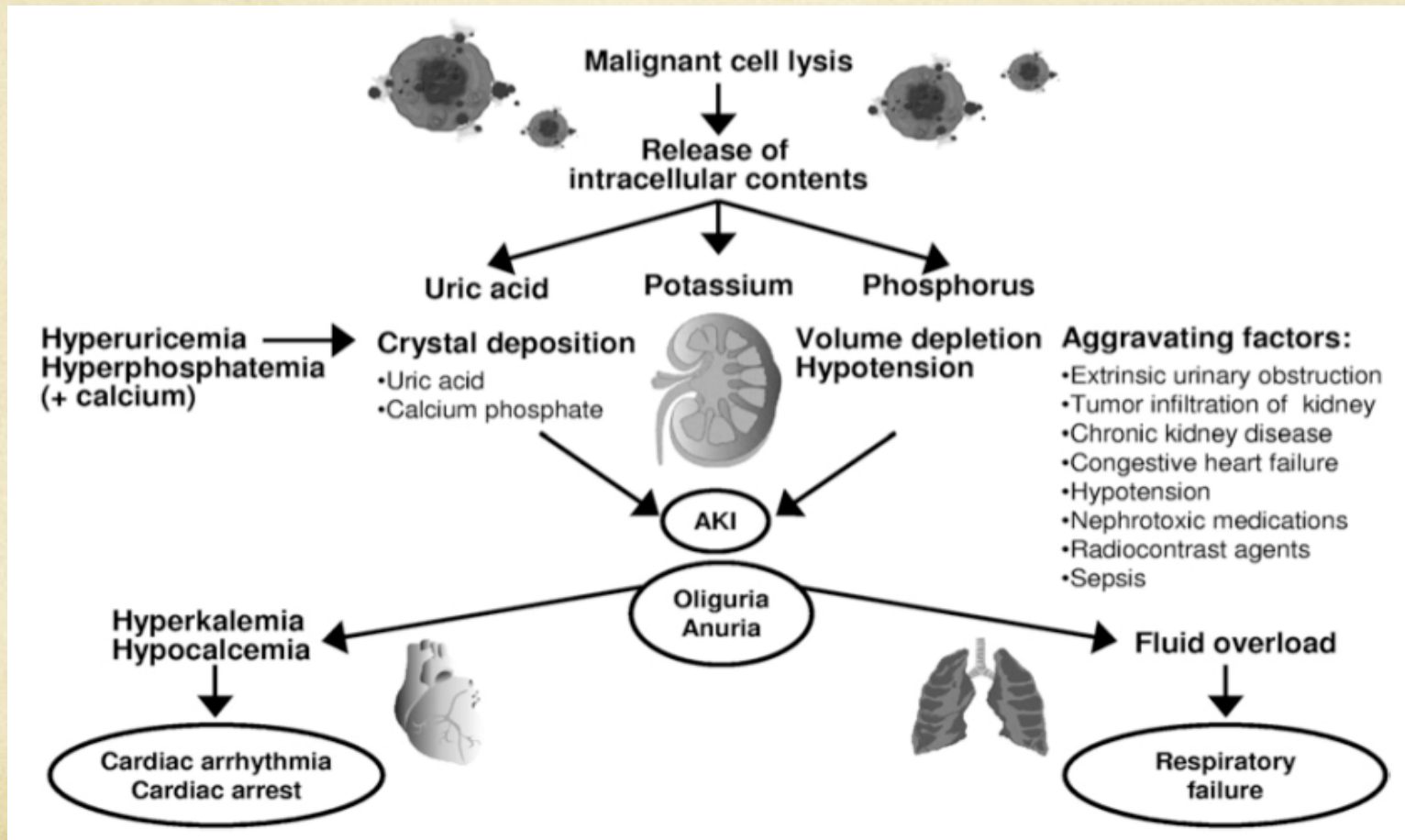
Pathophysiology

- Purine nucleic acids, which are also released by cell breakdown, are ultimately metabolized to uric acid (UA) by xanthine oxidase.
- With a pKa of 5.6, UA precipitation is enhanced by high acidity and high concentration in the renal tubular fluid, becoming less soluble as renal tubule pH decreases.
- Renal medullary hemoconcentration and decreased tubular flow rates, from volume depletion, also contribute to crystallization.

Pathophysiology

- Another cause of AKI is acute nephrocalcinosis from CaP crystal precipitation.
- CaP precipitation is exacerbated by overzealous iatrogenic alkalinization in an attempt to prevent UA crystallization.
- Precipitation of xanthine, which is even less soluble in urine than UA, has also been reported to contribute to AKI in those treated with allopurinol.

Pathophysiology



Treatment



Volume Repletion/Expansion

- Volume depletion can further increase the risk of UA and CaP precipitation.
- Volume repletion/expansion maintains renal blood flow and urine flow, promoting urinary excretion of K, UA, and phosphate.
- Recommended in patients at intermediate and high risk of TLS.
- Recommended that IVF should be started 24-48 hours before chemotherapy at a rate of 80-100 mL/m²/hr in adults to achieve urinary volumes of >3L/d.

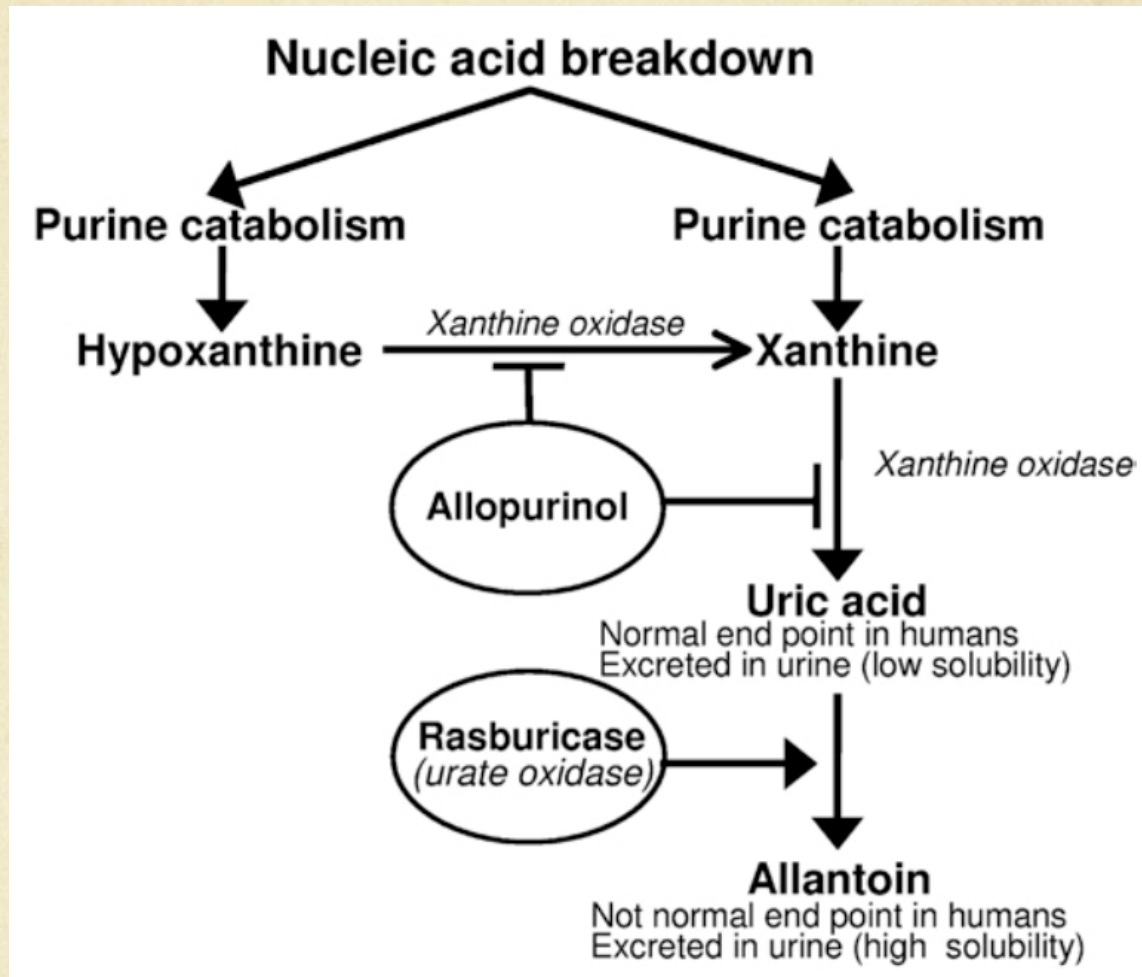
Urinary Alkalinization

- Historically, the goal of urinary alkalinization is to maintain urinary pH at 6.5-7.5 to enhance uric acid solubility, therefore promoting its excretion.
- Xanthine solubility increases to a much lesser degree in alkaline urine given its higher pKa (7.7) compared with uric acid.
- Studies in rats have demonstrated that in the absence of increasing urinary flow rates, increasing urinary pH greater than 7.0 was ineffective in preventing UA crystallization.
- Given the lack of demonstrated efficacy and the potential complications of iatrogenic metabolic alkalosis and enhancing CaP precipitation, current Heme/Onc guidelines do NOT recommend urinary alkalinization in the prevention and treatment of TLS.

Conger et al. J Clin Invest, 59:p786, 1977.

Coiffier B et al. J Clin Oncology. 26:p2767, 2008.

Allopurinol vs Rasburicase



- Allopurinol blocks xanthine oxidase enzymatic actions by competitive inhibition, thereby preventing the new synthesis of UA.
- Rasburicase is a recombinant urate oxidase that increases the rate of UA catabolism to allantoin, which is highly soluble and easily excreted

The Case for Rasburicase... GRAALI

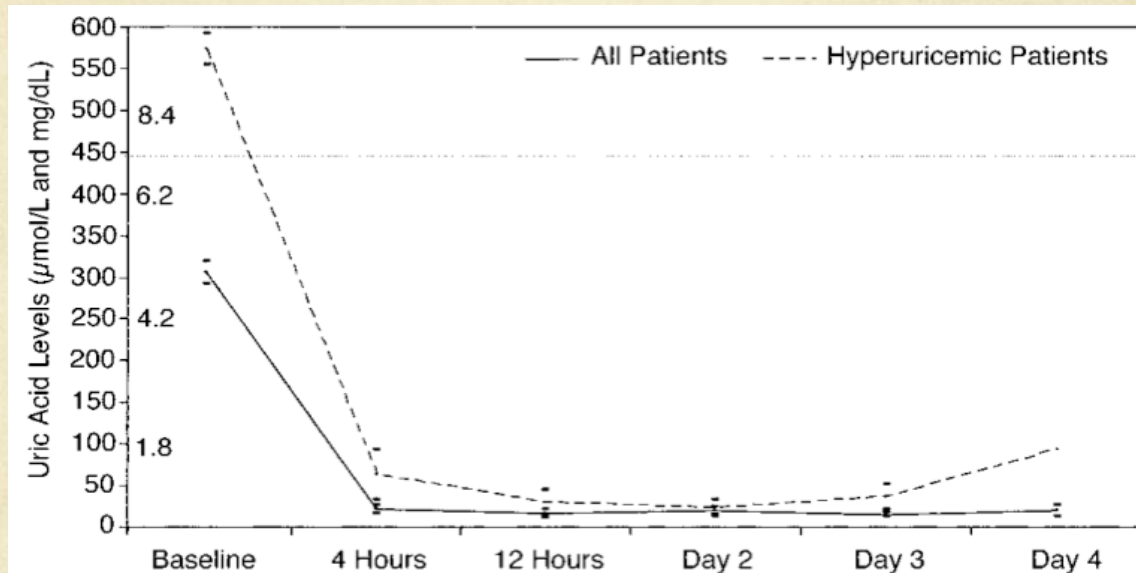
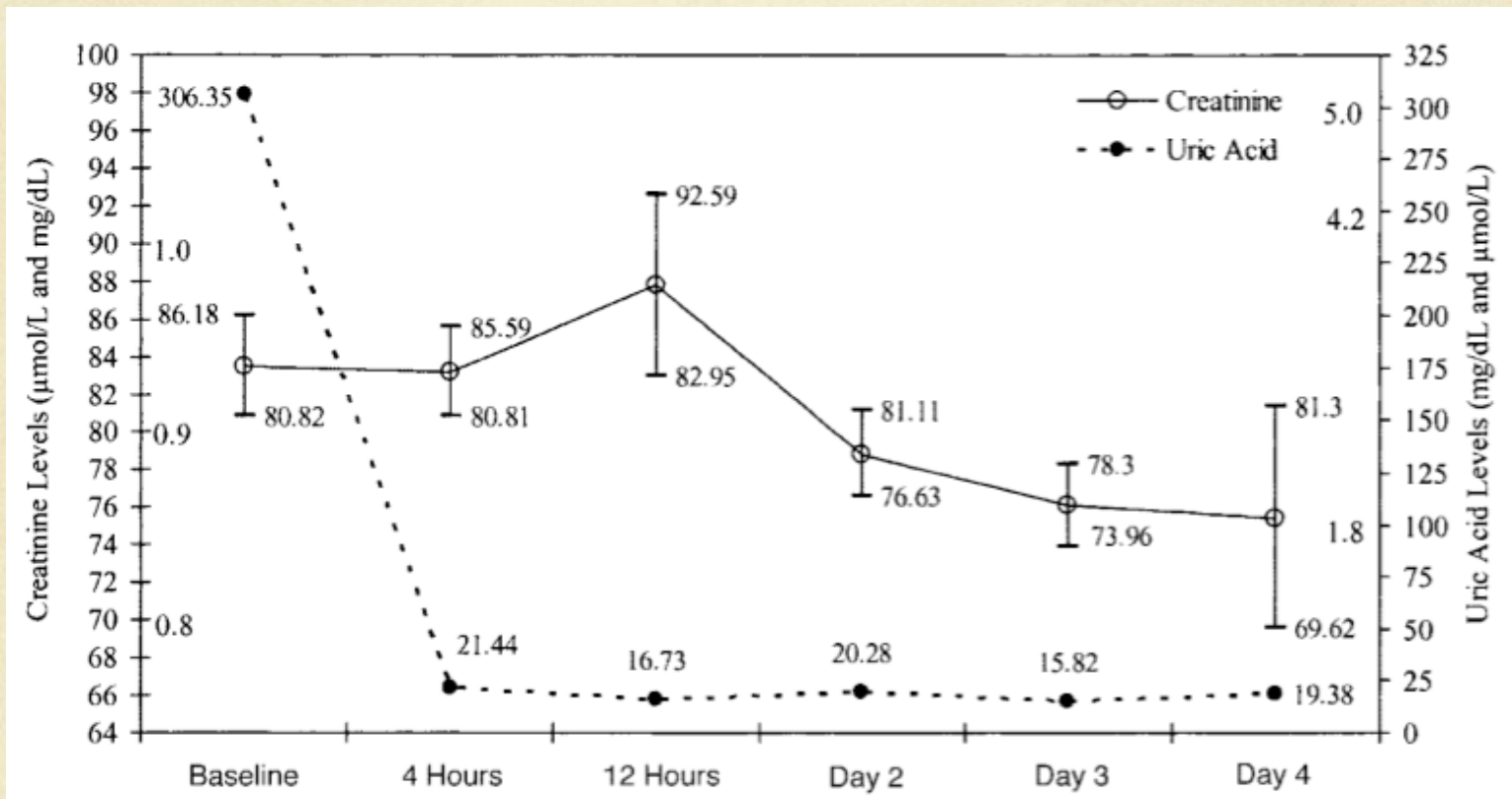


Fig 2. Average uric acid levels (\pm standard error of the mean) during treatment with rasburicase. Hyperuricemia is defined as uric acid $> 450 \mu\text{mol/L}$ (7.56 mg/dL).

- A single-arm, open-label study conducted in 100 adults with aggressive non-Hodgkin lymphoma, patients were treated prophylactically with rasburicase.
- Control of UA was obtained within 4hrs of injection of the drug.

GRAALI



- No case of AKI was reported at seven days, no long term follow up data was reported.

The Case for Rasburicase...

- An pediatric study of 235 patients with newly diagnosed B-cell non Hodgkin lymphoma/B-ALL was conducted to study the efficacy of standard-intensity therapy or reduced-intensity therapy.
- The incidence of AKI, need for dialysis, and TLS were significantly lower in the French cohort compared with the US cohort (11% vs 27%, 3% vs 15%, and 9% vs 26%, respectively).
- Although the cohorts were not randomized, the authors suggest that the differences were the result of the French Cohort having access to nonrecombinant urate oxidase for the management of hyperuricemia, whereas patients in the United States were treated with only allopurinol.

Allopurinol vs Rasburicase

- There have been two phase 3 randomized control trials prospectively comparing the efficacy of allopurinol versus rasburicase in hyperuricemia.
- Although both studies showed that addition of rasburicase decreased UA levels more rapidly than allopurinol alone, one study was not powered to find a difference in AKI and dialysis rates, while the other did not report the effect of these therapies on kidney function.

The Case for Rasburicase... ?

- FDA has approved the use of rasburicase for both the adult and pediatric cancer patients at risk for hyperuricemia.
- Daily cost of a standard dose of rasburicase in a 70 kg patient is approximately \$4400. (Recommended course is 5 days)
- Consideration: Recent case series have suggested lower doses with shorter schedules have been equally efficacious as compared to FDA-approved doses.
- Consideration: Reports suggest that since the introduction of rasburicase, the need for dialysis has “dramatically” declined which may justify rasburicase use from a cost-effectiveness standpoint.

Renal Replacement Therapy and Prevention of TLS

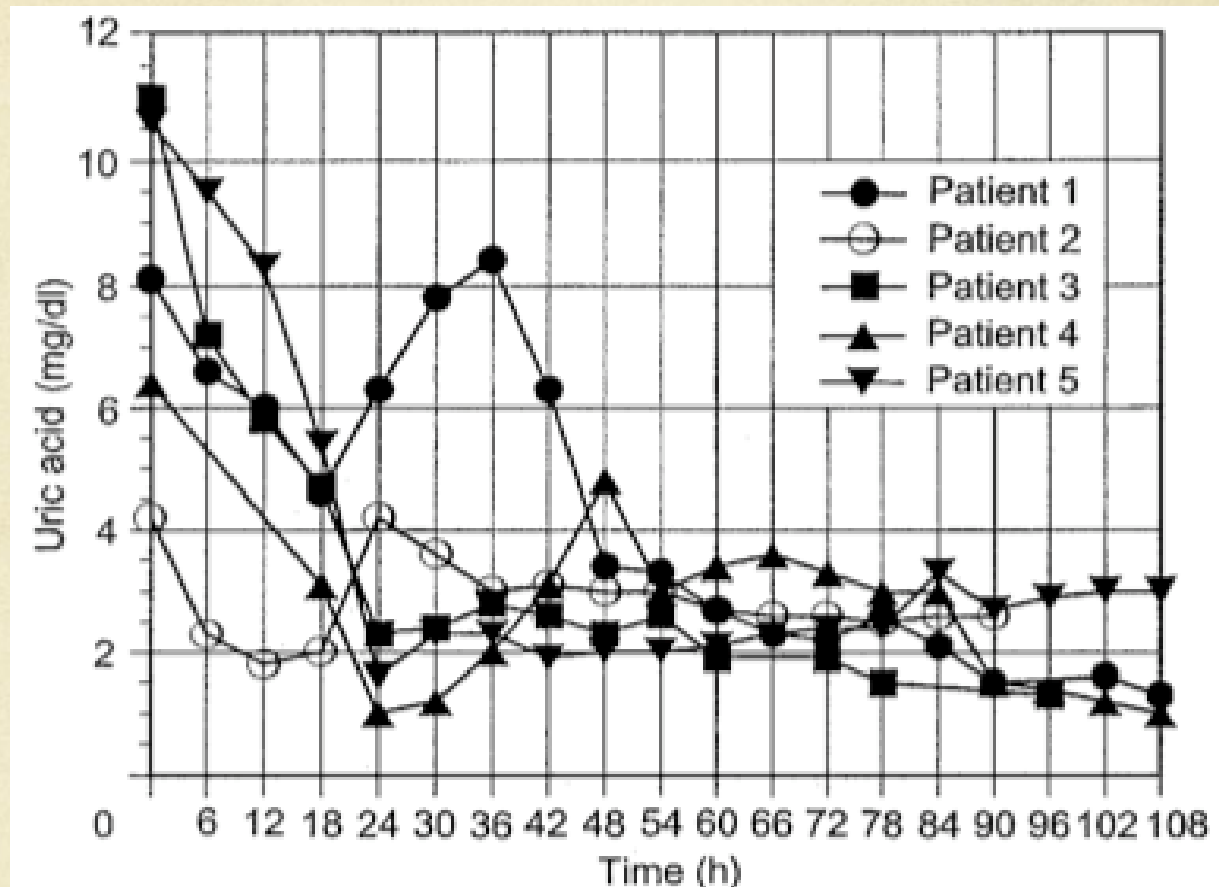
RRT

- Indications for RRT in TLS are the same for any other disorder (electrolyte abnormalities, volume overload, uremia, etc.).
- Although there are no studies evaluating and comparing outcomes of intermittent HD and CRRT, some recommend following HD with CRRT to prevent rebound electrolyte abnormalities.
- The use of prophylactic RRT in patients at risk of TLS has not been well studied.

Saccente et al.

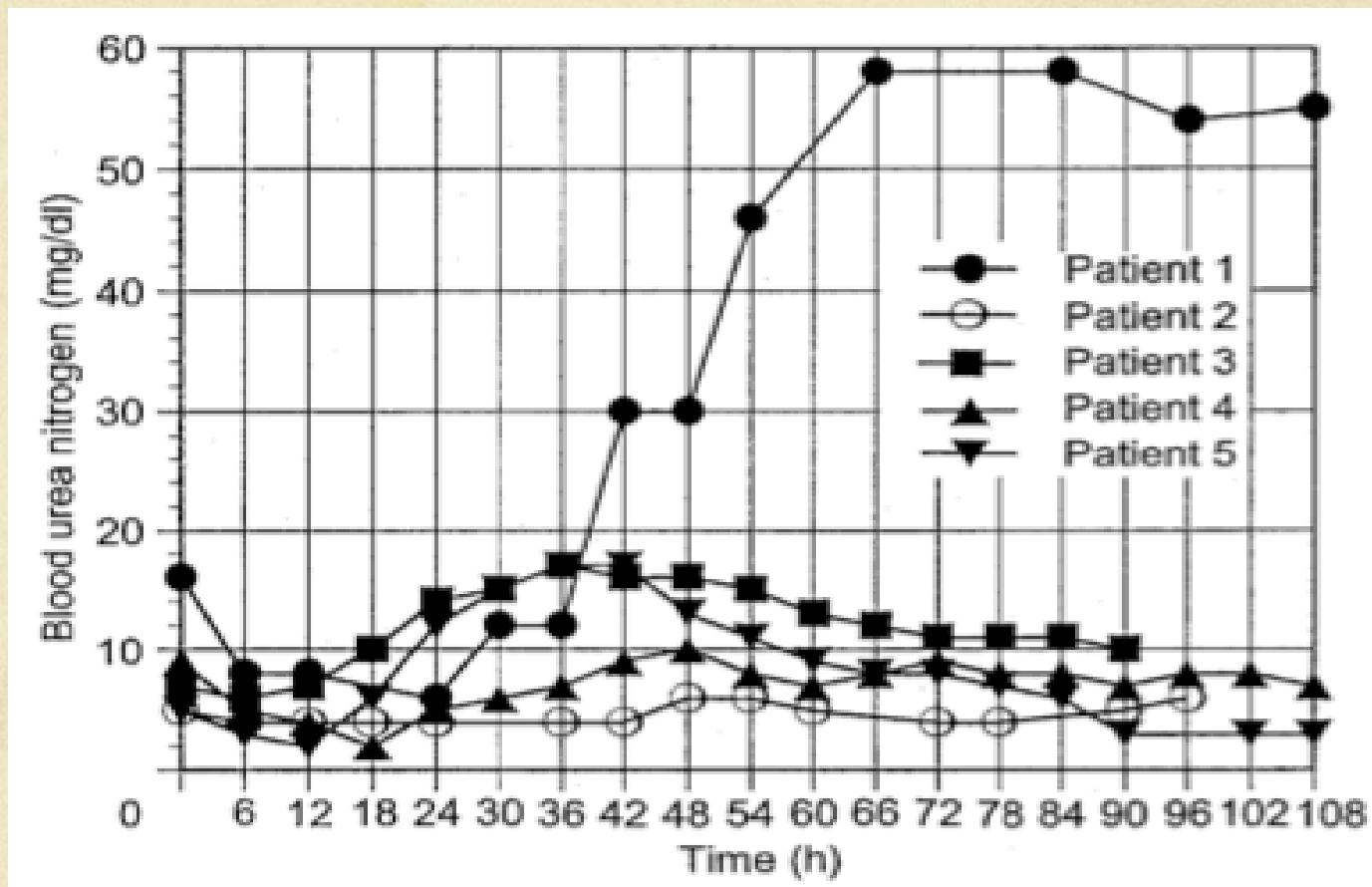
- Prospective use of CVVH, in addition to conventional management to prevent renal failure from TLS, in five children with advanced Burkitt lymphoma and T-cell ALL.
- Full-dose induction chemotherapy was begun within 24 hr of diagnosis.
- CVVH was begun at a mean time of 10.5 hr before chemotherapy was initiated.

Saccente et al.



- After beginning CVVH, the UA levels decreased 46% prior to beginning chemotherapy to a mean of 4.2 mg/dl 24 hrs after chemotherapy was initiated.

Saccente et al.



- After beginning chemotherapy, CVVH was continued for a mean of 85 hr (range 70-91 hr).
- Four of the five patients had either no change or a drop in the serum Cr.
- In patient 1, BUN peaked at 58 mg/dl and the Cr at 4.7 mg/dl six days after beginning chemotherapy with a subsequent return to normal (CVVH filter clogged).

Choi et al.

- Retrospective study evaluated the efficacy of CVVH with induction chemotherapy in 11 patients with Burkitt lymphoma at a high risk of developing TLS.
- Seven patients had spontaneous TLS and four patients were at a high risk of TLS.
- CVVH was applied to all patients before chemotherapy or within 2 hr of chemotherapy.
- CVVH was continued for 109 hr (range 70.5-157.5).
- The median follow-up was 19.7 months (range 1-97.8).
- No patient had fatal metabolic complications related to TLS.
- The 1-year event-free survival and overall survival rates were both 82% (9 of the 11 patients).
- As a comparison, similar studies with high-risk populations report 1-year event-free survival rates and 1-year survival rates were 39% and 70%, respectively.

Thank You